PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
Fod3 im		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO97/00074	12/03/1997	13/03/1996
International Patent Classification (IPC) or national classification and IPC		
A61K39/00		
Applicant		
FODSTAD, Oystein et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 34 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/10/1997	20. 05. 98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Herrero, M Telephone No. (+49-89) 2399-8542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NO97/00074

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-32	as received on	10/03/1998	with letter of	09/03/1998

Claims, No.:

1-13	as received on	10/03/1998	with letter of	09/03/1998

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-8.

because:

☒ the said international application, or the said claims Nos. 6-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

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☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8, 10, 13
	No:	Claims	9, 11
Inventive step (IS)	Yes:	Claims	1-8, 10, 13
	No:	Claims	9, 11
Industrial applicability (IA)	Yes:	Claims	1-5, 9-13
	No:	Claims	6-8 (?). See Section III

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

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SECTION III

The subject-matter of Claims 6-8 does not require an international preliminary examination, as it relates to methods for treatment of the human or animal body by therapy (Rule 67.1(iv) PCT). For the assessment of the present claims 6-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1 = Lemoli, R.M. et al (1994) Bone Marrow Transplant **13**:465-471 (Abstract)
D2 = Myklebust, A.T. et al (1994) Cancer Res. **54**:209-214 (Abstract)
[Cited in the application, cf page 30, reference 14]
D3 = Tecce, R. et al (1991) Int. J. Cancer **49**: 310-316 (Abstract)
D4 = WO 91/09058
D5 = Tonevitsky, A.G. et al (1986) Int. J. Cancer **37**:263-273 (Abstract)

2.2 In view of the priority documents pertaining to the present application, the scientific publication by Kvalheim, G. et al (1996) J. Hematother. **5**:427-436, cited in the search report under the P category, is not to be regarded as state of the art according to Rule 64 (1) PCT as the date of priority of 13.03.96 is validly claimed.

2.3 Relevant disclosures of the cited documents:

- D1 describes purging tumour cells from bone marrow; immunodepletion of neoplastic cells with immunotoxins directed toward the lymphoid-associated antigens CD30 and CD2 and containing saporin.

- D2 describes purging breast cancer cells from bone marrow with immunotoxins constructed as conjugates of monoclonal antibodies (MoAb) reactive with antigens abundantly expressed on human carcinoma cells and Pseudomonas exotoxin A.

- D3 describes purging autologous bone marrow prior to transplantation in patients suffering from monocytic leukemia with 2 monocytic-cell-lineage-specific immunotoxins constructed with saporin and 2 MoAbs of high specificity for circulating monocytes and M5b acute nonlymphoid leukemia (ANLL).

- D4 describes immunotoxins comprising the myelomonocytic specific MoAb 195 useful for purging ANLL from bone barrow, see e.g. page 9, lines 13-17; page 52, first full paragraph and page 130, lines 20-26.

- D5 describes purging murine erythroleukemic stem cells from bone marrow employing an immunotoxin comprising a conjugate of ricin-A-chain and MoAb MAE15 which binds to the surface of normal and neoplastic murine erythroid cells: a model for studies of bone-marrow transplantation therapy.

2.4 Novelty and inventive step (Article 33(2) and (3) PCT)

(a) In the light of the supporting description and the available prior art, present Claims 1-8, 10 and 13 would appear to relate to novel and inventive subject-matter which accordingly satisfies the criteria set forth in Article 33(2) and (3) PCT.

In this regard, the hereby disclosed synergistic effect brought about by the combination of the immunotoxins denominated MOC31-PE and BM7-PE on the selective killing of human breast cancer cells in a cell population of a stem cell

transplant harvested from peripheral blood (see e.g. page 11, lines 1-31 and Table 4 on page 17), is considered a finding not obviously derivable from the available prior art.

(b) Notwithstanding the above, the application does not satisfy the criteria set forth in Art. 33(2) and (3) PCT because, under its present wording, the subject-matter of Claims 9 and 11 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and/or does not involve an inventive step (Rule 65(1)(2) PCT).

As presently characterized the immunotoxins claimed *per se* in Claim 9 as well as their use according to Claim 11, appear to be anticipated and/or rendered obvious by the related disclosures of D2 which, for the purpose of eliminating breast cancer cells from human bone marrow, analyses the effect of the combination of immunotoxins therein denominated MOC31-PE and NrLU10-PE.

SECTION VII

Although the corresponding indications of the Applicants in their reply letter of 09.03.98 have been taken into account, it is pointed out that no adequate evidence has still been provided suitable to ascertain whether the specific MoAbs referred to in the claims are in fact publicly available, e.g. deposited (i.e. the statements in page 15, lines 7-11 of the application as originally filed do not necessarily imply the free availability of the concerned antibodies).

SECTION VIII

1. The wording of independent Claim 1 is open to interpretation, contrary to Article 6 PCT. The claim should have more accurately characterized the two required immunotoxins, indicating, e.g., that each immunotoxin is composed of a conjugate between an antibody and a cell toxin, //... //, wherein one of the antibodies targets an (abundantly expressed) epitope of the antigen EGP2 expressed by the gene

GA733-2 and the other antibody is directed to an epitope of the antigen expressed by the genes MUC1, MUC2 or MUC3 or a combination of these...

2. The above objection (Art. 6 PCT) also affects the broadly formulated independent claims 9, 11 and 13, insofar as none of these claims unambiguously defines the nature of the two distinguishing specific immunotoxins required to carry out the invention.

3. Moreover, in concordance with the underlying inventive concept, Claims 9 and 10 should have been directed to, e.g., "A preparation of two immunotoxins..." (see independent Claim 13). For the same reason Claim 11 should have been directed to the "Use of a preparation of two immunotoxins..."

4. The arbitrary denominations MOC31, BM7, BM2, 12H12 and 595A6, do not embrace any well recognized meaning and consequently the scope of Claims 2-5 and 10 is rendered unclear, contrary to Art. 6 (PCT) (see in this regard the comments on the above Section VII).

5. The following appear to be clerical mistakes:

Page 2, line 6: "initally"; page 3, line 10:"woth"; page 10, line 21 should read "are" instead of "is"; page 20, line 16: "intial"; page 28, line 19: "immuntoxin" and "th".

It appears that Claim 1 should have referred to gene GA733-**2** (cf page 11, lines 23-24 and page 12, lines 4-5). Moreover, Claim 1 reads "Pseuctomonas", Claim 4 "anitbodies" and Claim 5 "characterzied". Seemingly Claim 10 was meant to read 595**A6** (see Claim 5) and Claim 13 should have been Claim **12.**

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 October 1997 (23.10.97)	
International application No. PCT/NO97/00074	**Applicant's or agent's file reference** FOD £ TV
International filing date (day/month/year) 12 March 1997 (12.03.97)	**Priority date** (day/month/year) 13 March 1996 (13.03.96)
Applicant FODSTAD, Øystein et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   09 October 1997 (09.10.97)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer I. Britel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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(PCT Article 36 and Rule 70)

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Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Herrero, M Telephone No. (+49-89) 2399-8542

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- ☒ claims Nos. 6-8.

because:

- ☒ the said international application, or the said claims Nos. 6-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

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see separat sh et

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